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# The relationship between terminal QRS distortion on initial ECG and final infarct size at 4 months in conventional ST- segment elevation myocardial infarct patients

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**Abstract**

**Background:** In the Sclarovsky-Birnbaum Ischemia Severity Grading System for patients with ST-segment elevation myocardial infarction (STEMI), "Terminal QRS distortion" is considered as "Grade III". This evidence for most severe ischemia is associated with cardiovascular magnetic resonance imaging (CMR) markers of myocardial damage in the subacute phase. Our aim was to assess whether terminal QRS distortions on the initial electrocardiogram (ECG) is predictive for infarct size (IS) and left ventricular ejection fraction (LVEF) at 4 months in anterior versus infarct locations.

**Methods:** Patient data of the HEBE, GIPS III and MAST, were pooled. ECGs of 411 STEMI patients were classified as absence (Grade II) or presence (Grade III) of terminal QRS distortion according to Sclarovsky-Birnbaum grading. CMR was performed at approximately 4 months and included IS and LVEF.

**Results:** Grade III ischemia was present in 142 of 411 (35%) patients and was more frequently observed with inferior STEMI ($P = 0.01$). In the total cohort and in anterior STEMI, no difference in LVEF or IS was observed between the two Grades. Whereas, in inferior STEMI Grade III was associated with a larger IS ($P < 0.01$) and also, a trend towards a lower LVEF was observed ($P = 0.09$).

**Conclusion:** In inferior STEMI, terminal QRS distortion on the initial ECG is associated with a larger IS at approximately 4 months, and can be used to identify a high-risk population in the acute phase. Also, a Grade III was associated with a trend towards a lower LVEF.



*Keywords:* Electrocardiography; QRS distortion; Myocardial infarction; Magnetic resonance imaging

## Introduction

The introduction of primary percutaneous coronary intervention (PPCI) has resulted in an improved survival in ST-segment elevation myocardial infarct (STEMI) patients, and has also resulted in smaller infarct size (IS), less remodeling, less impaired LVEF and less heart failure [1,2]. Identifying markers that aid early risk-stratification in STEMI is critical to determine optimal treatment strategies and to improve outcome. The electrocardiogram (ECG) remains a cornerstone diagnostic modality in STEMI patients and thus identifying a prognostic ECG marker as a risk-stratifying tool is both feasible and clinically applicable.

In STEMI, changes in the terminal portion of the QRS during only most severe ischemia have previously been described, and are believed to be caused by prolongation of the electrical conduction in the myocardium in the ischemic zone [3,4]. These QRS changes, specifically absence or occurrence of terminal QRS distortion, can be classified according to the to the "severity

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of ischemia" by Sclarovsky and Birnbaum (SB) [5]. There are different criteria for application in the ECG leads revealing the acute changes in anterior versus inferior STEMI locations: the "disappearing S wave criterion" for anterior and the "small R wave to ST ratio" for inferior STEMI. Although this grading system was initially developed in the thrombolysis era, several studies have shown its prognostic value in PPCI treated STEMI. Grade III ischemia on initial ECG has been shown to be associated with less myocardial salvage, more microvascular obstruction (MVO), increased infarct size (IS) and 30-day mortality [5–9]. Previous studies have assessed its predictive value for Cardiovascular Magnetic Resonance imaging (CMR) markers of myocardial infarction assessed in the subacute phase. However, its predictive value on long term IS and left ventricular ejection fraction (LVEF) has not yet been investigated.

The primary objective of the current study, is to assess whether the severity of ischemia on initial ECG, as classified by the SB ischemia grading system, can be used to predict LVEF and IS at approximately 4 months on CMR, for different infarct locations.

## Methods

### *Study population*

For the current analysis patient data were pooled from the previously published HEBE, GIPS III and MAST study [10–14], which all performed CMR approximately 4 months following infarction.

In brief, the HEBE trial was designed to assess the effect of bone marrow cell therapy on cardiac improvement in STEMI patients assessed with CMR. A total of 200 patients that were successfully treated with PPCI between August 2005 and April 2008, were included in a randomized, multi-center, open trial with blinded evaluation of endpoints [10,11].

The GIPS III trial, was designed to determine whether metformin treatment following STEMI in patients without diabetes preserves LVEF at four months as assessed with CMR. A total of 380 patients who underwent PPCI between January 2011 and May 2013 at the University Medical Center Groningen, the Netherlands, were enrolled [12,13].

In both the HEBE and GIPS III trial, the effects of treatment on systolic myocardial function following STEMI were neutral.

The MAST study was a prospective observational cohort study of 89 consecutive first STEMI patients who underwent successful PPCI between 2006 and March 2008 at the Maastricht University Medical Center, the Netherlands. The principal investigator of the GIPS III, HEBE and MAST study were approached and consented to collaborate in a patient level pooled analysis. The requested data was provided and they vouched for the correctness of the data. All studies were conducted in accordance with the Declaration of Helsinki and the study protocol was approved by institutional review boards of the participating centers.

These studies included patients with a new ST elevation at the J point in at least 2 contiguous leads of $\geq 2$ mm (0.2 mV) in men or $\geq 1.5$ mm (0.15 mV) in women in leads V2–V3 and/or of $\geq 1$ mm (0.1 mV) in other contiguous chest leads or the limb leads.

For this post-hoc ECG and CMR analyses the following additional in- and exclusion criteria were applied. Patients were considered eligible if there was an available initial pre-reperfusion ECGs (in-ambulance, in-hospital or at the catheterization laboratory) and LVEF was assessed by CMR imaging at follow-up. Additional exclusion criteria for this analysis were: re-infarction prior to CMR imaging, inverted terminal T-waves, intraventricular conduction delay $\geq 120$ milliseconds QRS duration (left or right bundle branch block), any ventricular rhythm, or a ventricular paced rhythm on the initial pre-PPCI ECG.

### *ECG analysis*

A standard 12-lead ECG was recorded at baseline prior to PPCI, either in-ambulance or in-hospital at a paper speed of 25 mm/s and a sensitivity of 10 mm/mV.

ECGs were analyzed in a blinded fashion by observer (M.H.) after having completed comparison of the initial 40 ECGs with an experienced observer (G.W.) on the SB severity of ischemia grading system. In case of disagreement, a consensus was reached by re-evaluating the ECGs.

The refined SB Ischemia grading system as previously described by Billgren et al. was used to categorize patients into either Grade II or Grade III ischemia [5].

In patients with inferior STEMI location indicated by ST-segment elevation primarily in leads II, III and aVF, Grade II was defined as a J point to R wave amplitude ratio $< 0.5$ and Grade III when this ratio was $\geq 0.5$. Whereas, in patients with anterior STEMI indicated primarily by ST-elevation in leads V1, V2 and V3, Grade II was defined as ST-elevation with an S wave below the isoelectric line and Grade III when ST elevation was present without an S wave below the isoelectric line.

### *Cardiovascular*

#### *Magnetic Resonance Imaging acquisition and analysis*

CMR was performed on a 1.5 or 3-T clinical CMR-scanner at $115 \pm 15$ days following PPCI. CMR imaging protocols for all three studies have been published previously [10,12,14]. In short, both cine and delayed contrast-enhanced CMR were performed in all studies to assess LVEF and IS.

On the cine short-axis images endocardial and epicardial contours were manually traced on short-axis cine, excluding papillary muscles, in the end-diastolic and end-systolic phases to determine end-diastolic volume (LVEDV, ml), end-systolic volume (LVESV, ml) and LVEF(%). LVEDV and LVESV were subsequently indexed for body-surface area.

Late gadolinium enhancement images were obtained 10–15 min after administration of a gadolinium-based contrast agent using an inversion-recovery, gradient-echo pulse sequence, with slice position identical to the cine images. Infarct location could subsequently be identified as hyper-enhancement and outlined. Summation of the volumes per slice of areas of hyperenhancement, allowed calculation of absolute IS (grams) and as a percentage of LV mass (% LV).

In all studies, the CMR data were analyzed using a dedicated software package and observers were blinded to clinical data.

*Statistical analysis*

Normally distributed data are expressed as mean ± SD and for non-normal distributed data the median value (Q1-Q3) is provided. Categorical variables are presented as number (%) and compared using the chi-square test. A Student's t- test or a 1-way analysis of variance was used to compare data with a normal distribution of continuous variables and a Mann–Whitney U test for non-normal distributed continuous variables.

LVEF(%), IS (in grams and % LV), LVEDVindex (ml/m$^2$) and LVESVindex (ml/m$^2$) were compared between patients with Grade II and Grade III ischemia by using a Mann–Whitney U test. This was assessed in the total STEMI study population, anterior vs. inferior STEMI.

A P value <0.05 was considered statistically significant. All statistical analysis were performed using SPSS software (version 22.0; SPSS Inc., Chicago, Illinois).

## Results

In total 421 patients underwent CMR imaging at follow-up and had a suitable pre-PPCI ECG (Fig. 1). However, ten patients experienced a re-infarction prior to CMR and were excluded. The current study thus included 411 patients. A severe Grade of ischemia (Grade III) was identified in 142 (34.5%) patients, whereas 269 (65.5%) patients had a Grade II ischemia. (See Fig. 2).

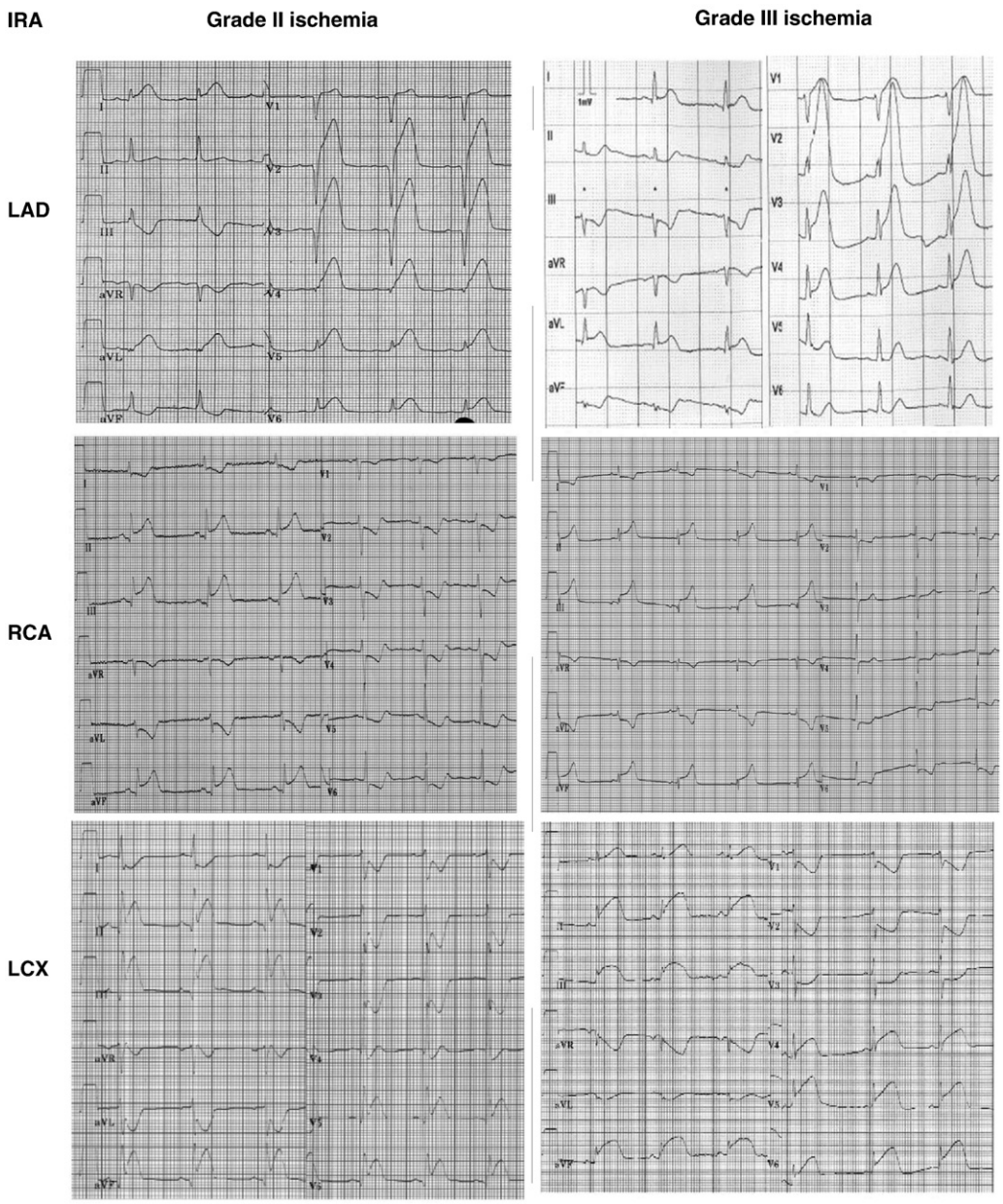


Fig. 1. Grade II and III of ischemia in different infarct-related arteries. The patient in the LCX Grade II example had a dominant LCX artery.IRA, infarct related artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

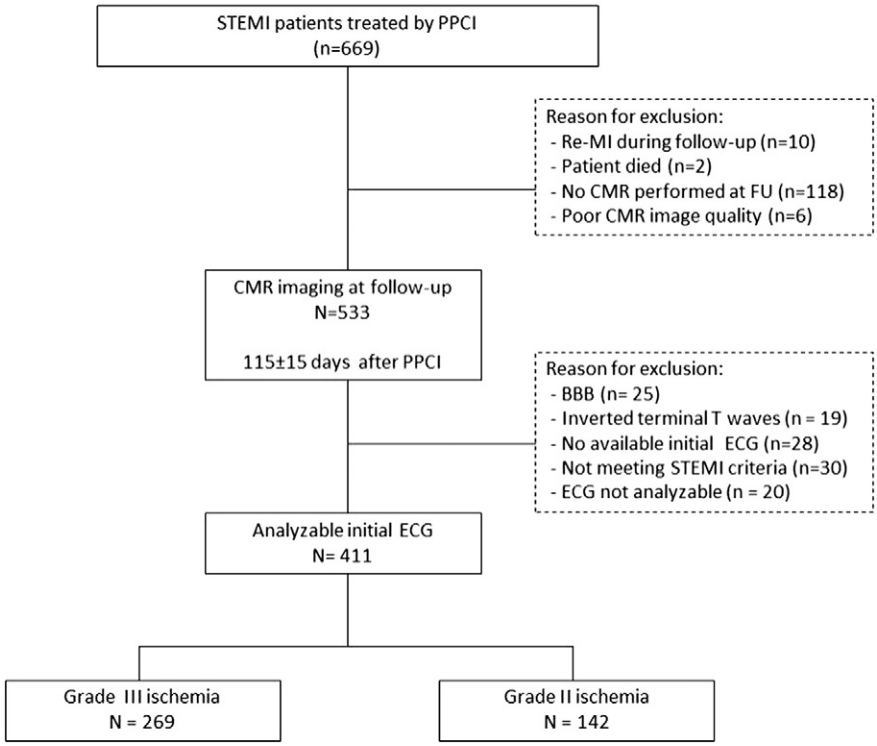


Fig. 2. Flowchart of included patients. STEMI, ST-elevation myocardial infarct; PPCI, primary percutaneous coronary intervention; re-MI, re-myocardial infarction; CMR, cardiovascular magnetic resonance imaging; FU, follow-up; BBB, bundle branch block; ECG, electrocardiogram.

Baseline characteristics of the total STEMI population and in the Grade II and Grade III groups are depicted in Table 1. Mean age was 57 ± 11 years and the majority of the included patients were male (80.5%). Grade III ischemia was more frequently observed when the IRA was the right coronary artery (RCA) (P = 0.01) and in the presence of multivessel disease (P = 0.03). Whereas, Grade II ischemia was more often observed when the left anterior descending artery (LAD) was the IRA. Time from symptom onset to PPCI did not differ between the Grade II and Grade III ischemia (P = 0.21).

As for LVEF and IS, no difference was observed between the two grades in the total STEMI population (Table 2). In a sub-analysis of the different infarct locations, IS and LVEF did not differ between the two Grades of ischemia in anterior STEMI patients (Fig. 3). However in inferior STEMI, Grade III ischemia was associated with a larger IS (P < 0.01). In the inferior STEMI group, Grade III on the initial ECG was associated with a larger IS at 4 months and a trend towards a lower LVEF (Table 2).

## Discussion

To the best of our knowledge, the current study is the first to assess whether the SB Grade of ischemia severity on initial ECG can be used as an ECG marker for IS and LVEF at 4 months following STEMI. We assessed the impact of the Grade of ischemia for the entire cohort, and also according to infarct location. The main finding of our analysis is that terminal QRS distortion in Grade III on initial ECG can be used as an ECG marker for IS at 4 months in inferior STEMI patients. This is a relevant finding considering that final IS by CMR assessed 3 months following STEMI has been shown to be an independent predictor for all-cause mortality and admission for heart failure [15]. Also, a trend towards a lower LVEF was observed in patients with a Grade III. Whereas, the Grade of ischemia was not associated with IS or LVEF at 4 months in anterior STEMI patients. In the total STEMI population, no difference in IS and LVEF was observed between both Grades of ischemia.

Several studies have investigated the association between the severity of ischemia on initial ECG and IS on CMR following STEMI [8,9,16,17]. However, in these studies CMR was performed within one week and up to 10 days following STEMI. In all studies Grade III ischemia was associated with a larger IS, less myocardial salvage and more microvascular obstruction.

In our study the severity of ischemia was not associated with a different LVEF at follow-up in the total STEMI population and in anterior STEMI, but was predictive in inferior STEMI. These results are in accordance with the study by Weaver et al., where an association was observed between the Grade of ischemia and larger IS among patients with inferior infarcts, but no association was found in anterior STEMI patients [8] Several other studies on the grade of ischemia and myocardium at risk have also reported discrepant results on the association observed in different IRA's and infarct locations. However, in another study that included only anterior STEMI patients the severity of ischemia was found to be independently associated with a larger area at risk in anterior STEMI patients [16]. In the study by Rommel et al., that included both anterior and inferior STEMI patients, no difference in area at risk was

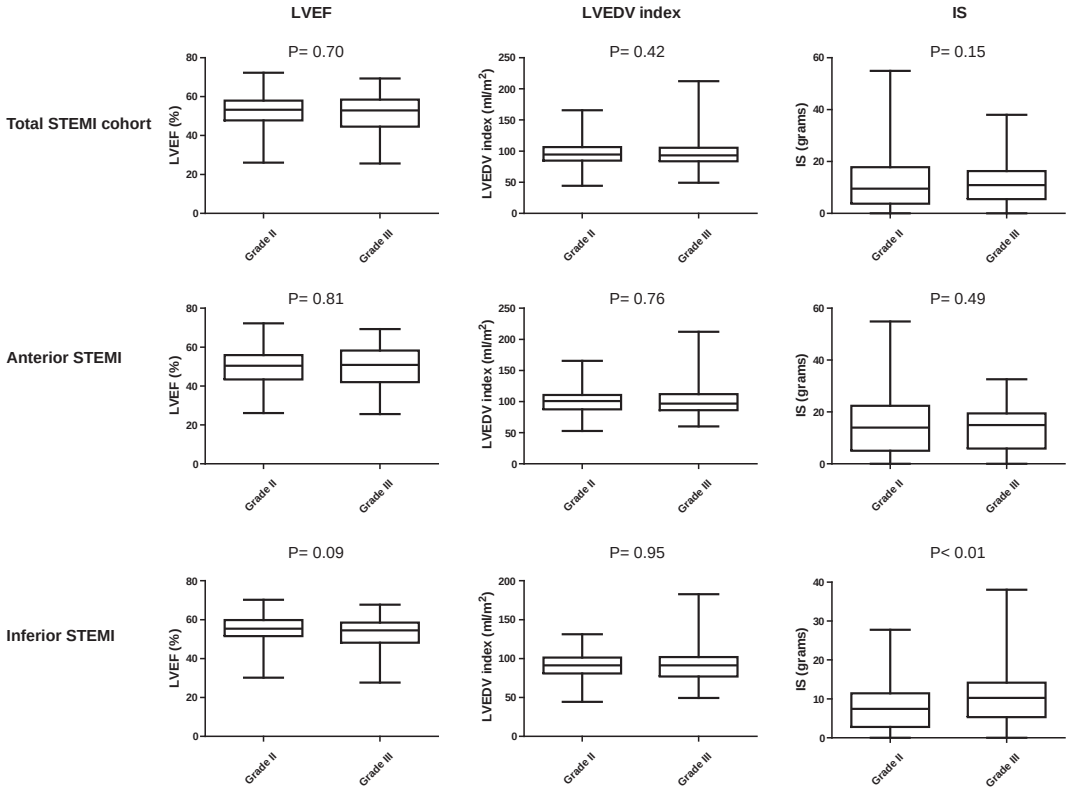


Fig. 3. Left ventricular function and infarct size in total cohort and separate for anterior and inferior STEMI. IRA, infarct related artery; RCA, right coronary artery; LCX, left circumflex artery; left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; IS, infarct size.

observed between Grade II and Grade III. They also reported no difference in LVEF measured within one week following STEMI. These results from previous studies suggest that the predictive value of the severity of ischemia may be different with respect to infarct location. Infarct location has previously been shown to be an independent predictor of IS and left ventricular ejection fraction [18,19]. Moreover, the criteria applied in the Sclarovsky-Birnbaum grading system differ for anterior and non-anterior patients.

When considering the criteria used for anterior vs. inferior STEMI, Grade III ischemia in anterior STEMI includes the absence of S wave below the TPinferior-PR isoelectric line in leads V1 to V3, whereas in inferior STEMI patients it is based on the J point to R wave amplitude ratio. In inferior STEMI patients it is questionable whether the criteria used for Grade II and Grade III in these patients is an actual expression of severe ischemia and not infarction. During ischemia the vector is directed towards the ischemic area and in patients with a RCA occlusion this would appear as an increased R wave in leads II, III and aVF. However, according to the Sclarovsky-Birnbaum grading system patients with a Grade III ischemia have a J-point to R wave amplitude $\geq 0.5$ and may be an expression of infarction rather than ischemia. Whether the Grade of ischemia in non-anterior patients is an actual marker of ischemia should be further investigated.

This difference in definition between Grade II and Grade III in anterior and inferior STEMI is the likely reason for the discrepant results observed in infarct size at 4 months between these infarct location groups. In patients with inferior STEMI, SB Grade III is based on criteria that most likely represents a larger infarct size at the time of admission ECG, and this difference persists after 4 months. However, in anterior STEMI patients, the SB grading of ischemia is based on criteria that most likely represent the severity of ischemia, and therefore would not necessarily be related to infarct size after 4 months. The final infarct size would be expected to be minimalized only in the anterior STEMI patients with a brief time to reperfusion, because of their more rapid progression of ischemia to necrosis. However, in the current study, since the median symptom onset to balloon time was approximately 3 h (mean 2.8 h; SD 2.0–4.0), no difference in final infarct size between those with initial Grade II versus Grade III would be expected.

Nevertheless, in the current study the Grade of ischemia holds a predictive value for assessing whether a patient will have a large IS and decreased LVEF at 4 months in inferior STEMI patients.

The advantage of the severity of ischemia grading is that it is an ECG score that can easily be assessed in the acute situation when important clinical decisions are being made. Whether the Grade of ischemia can guide management in clinical practice, such as in higher triage priority in countries where there is a long ambulance-to-hospital time delay or the use of adjunctive therapies, needs to be further investigated.

## Limitations

Several limitations should be mentioned. First, time to reperfusion is an important variable in the ischemia-infarction

Table 1
Baseline characteristics.

| | Total study cohort (N = 411) | Grade II ischemia (N = 269) | Grade III ischemia (N = 142) | *P*-value |
|---|---|---|---|---|
| Age (years) | 57 ± 11 | 56 ± 11 | 58 ± 10 | 0.17 |
| Male gender (%) | 331 (80.5) | 221 (82.2) | 110 (77.5) | 0.25 |
| BMI (kg/m2)* | 26.1 (24.2–28.7) | 26.2 (24.2–28.7) | 26.0 (24.2–28.7) | 0.85 |
| Risk factors (%) | | | | |
| Diabetes mellitus | 127 (30.9) | 87 (32.3) | 40 (28.2) | 0.31 |
| Current cigarette smoking | 218 (53.0) | 142 (52.8) | 76 (53.5) | 0.89 |
| Hypertension | 123 (29.9) | 76 (28.3) | 47 (33.1) | 0.31 |
| Dyslipidemia | 185 (45.0) | 116 (43.1) | 69 (48.6) | 0.18 |
| Family history of CAD¥ | 98/207 (47.3) | 57/130 (43.8) | 41/77 (53.2) | 0.19 |
| Previous PCI at baseline | 6 (1.5) | 3 (1.1) | 3 (2.1) | 0.49 |
| Angiography and infarct treatment | | | | |
| Time symptom onset to PCI (h) | 2.8 (2.0–4.0) | 2.8 (2.0–4.2) | 2.8 (1.9–3.7) | 0.34 |
| Infarct-related artery (%) | | | | |
| Left anterior descending artery | 190 (46.2) | 136 (50.6) | 54 (38.0) | **0.02** |
| Left circumflex artery | 56 (13.6) | 37 (13.8) | 19 (13.4) | 0.92 |
| Right coronary artery | 165 (40.1) | 96 (35.7) | 69 (48.6) | **0.01** |
| Multivessel disease (%) | 122 (29.7) | 70 (26.0) | 52 (36.6) | **0.03** |
| TIMI flow Grade pre-PCI | | | | |
| 0 | 259 (63.0) | 168 (62.5) | 91 (64.1) | 0.75 |
| 1 | 41 (10.0) | 28 (10.4) | 13 (9.2) | 0.69 |
| 2 | 59 (14.4) | 33 (12.3) | 26 (18.3) | 0.10 |
| 3 | 51 (12.4) | 39 (14.5) | 12 (8.5) | 0.08 |
| TIMI flow Grade post-PCI | | | | |
| 2 | 27 (6.6) | 21 (7.8) | 6 (4.2) | 0.16 |
| 3 | 383 (93.2) | 247 (91.8) | 136 (95.8) | 0.13 |
| Medication at discharge (%) | | | | |
| Salicylates | 401 (97.6) | 262 (97.4) | 139 (97.9) | 0.93 |
| Clopidogrel | 351 (85.4) | 223 (82.9) | 128 (90.1) | 0.06 |
| Ticagrelor | 56 (13.6) | 43 (16.0) | 13 (9.2) | **0.02** |
| Prasugrel | 1 (0.2) | 1 (0.4) | 0 (0) | 0.45 |
| Coumarine | 26 (6.3) | 15 (5.6) | 11 (7.7) | 0.40 |
| Beta-blockers | 396 (96.4) | 256 (95.2) | 140 (98.6) | 0.10 |
| ACE-inhibitor or AT II receptor blocker | 349 (84.9) | 223 (82.9) | 126 (88.7) | 0.14 |
| Statins | 408 (99.3) | 266 (98.9) | 142 (100) | 0.30 |

BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention; h, hours; TIMI, Thrombolysis in Myocardial Infarction; ACE-inhibitor, angiotension converting enzyme inhibitor; AT II receptor blocker, angiotensine II receptor antagonist.

* Missing in 204 patients. In GIPS study family history of coronary artery disease was not reported.

progress in acute STEMI and should be considered. However, the time symptom onset to PCI did not differ between Grade II and Grade III ischemia (P = 0.21; Table 1). Recent other studies have also observed no difference in symptom to balloon time between the two Grades of ischemia.

Second, the recruitment period differs between the three studies and treatment post STEMI may be different. Although the HEBE and MAST study overlap in recruitment period (2006–2008), the recruitment of GIPS III study was from 2011 to 2013. The difference in ticagrelor use at discharge between Grade II and Grade III ischemia groups is the result of patients included in the GIPS III study. However this would not have any influence on LVEF and IS.

Finally, in the current study we only included patients that underwent CMR at 4 months and therefore cannot rule out selection bias. Also, this analysis does not include STEMI equivalents. This could have also caused a potential selection bias in the results since it is possible that only patients with large ischemia vectors (associated with larger ischemic areas and potentially larger infarct sizes) were included. Further research is needed to assess the relationship between terminal QRS distortion on initial ECG and final infarct size in these patients.

## Conclusions

The Grade of ischemia is an rapidly and easily ECG marker predictive for IS and LVEF at 4 months in inferior STEMI patients. Also, a trend towards a lower LVEF was observed in inferior STEMI patients with a Grade III ischemia. The severity of ischemia can identify a high-risk patient population in the acute phase of STEMI and may aid in clinical management.

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Table 2
Left ventricular function and infarct size at 4 months.

| | Total study cohort | Grade II | Grade III | *P*-value |
|---|---|---|---|---|
| **All STEMI** | *n = 411* | *n = 269* | *n = 142* | |
| *LVEF* (%) | 53 (47–58) | 53 (48–58) | 53 (45–58) | 0.70 |
| LVEDV index (ml/m2) | 94 (84–106) | 94 (84–107) | 93 (84–106) | 0.42 |
| LVESV index (ml/m2) | 43 (35–55) | 44 (36–55) | 42 (34–56) | 0.51 |
| IS (grams) | 10 (4–17) | 10 (4–18) | 11 (6–16) | 0.36 |
| IS (% LV)[¥] | 0.3 (0.1–10.8) | 0.3 (0.1–9.4) | 1.7 (0.1–11.3) | 0.15 |
| **Anterior STEMI** | *n = 190* | *n = 136* | *n = 54* | |
| LVEF (%) | 51 (43–57) | 50 (43–56) | 51 (42–58) | 0.81 |
| LVEDV index (ml/m2) | 100 (87–111) | 101 (88–111) | 97 (86–112) | 0.76 |
| LVESV index (ml/m2) | 49 (38–61) | 50 (39–61) | 46 (35–64) | 0.57 |
| IS (grams) | 14 (6–21) | 14 (5–22) | 15 (6–19) | 0.49 |
| IS (% LV) | 2.6 (0.1–14.2) | 2.6 (0.1–14.2) | 3.6 (0.1–13.8) | 0.54 |
| **Inferior STEMI** | *n = 221* | *n = 133* | *n = 88* | |
| LVEF (%) | 55 (50–59) | 55 (52–60) | 55 (48–59) | 0.09 |
| LVEDV index (ml/m2) | 91 (80–102) | 91 (81–101) | 91 (77–102) | 0.95 |
| LVESV index (ml/m2) | 41 (34–48) | 41 (34–48) | 41 (33–49) | 0.54 |
| IS (grams) | 9 (4–13) | 7 (3–11) | 10 (5–14) | <**0.01** |
| IS (% LV) | 0.2 (0.1–8.0) | 0.1 (0–6.6) | 1.3 (0.1–9.9) | <**0.01** |

*Infarct size (gram) missing in 32 patients, including 26 in Grade II and in 6 in Grade III. Reported in Median (25th- 75th Percentile).
[¥]Infarct size (% LV) missing in 35 patients, of which 29 in Grade II and in 6 in Grade III.
STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; IS, infarct size.

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